**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: GRUENBERG

Serial No.: 08/700,565

Filed: July 25, 1996

For: AUTOLOGOUS IMMUNE CELL THERAPY; CELL COMPOSITIONS, METHODS AND APPLICATIONS TO TREATMENT OF HUMAN DISEASE

Art Unit: 1644

Examiner: Schwadron, R.



I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Assistant Commissioner for Patents,
Washington, D.C. 20231, on this date.

10/18/99
Date

Stephanie Seidman

#22 ELECTION
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**ELECTION**

Assistant Commissioner for Patents

Washington, D.C. 20231

Dear Sir:

Responsive to the Requirement for Election of species, mailed August 16, 1999, applicant elects the method of claims 155-173 directed to methods for generating a regulatory T cells, and further selects TH1 cells, with traverse, for search purposes. Claims 1-17, 22-35 and 154-210 read on the elected species. read on the elected species.

**REMARKS**

The fee for a one month extension of time may be charged to Deposit Account No. 08-1641. Any fees that may be due in connection with filing this paper may be charged to Deposit Account No. 02-4070. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

**Traverse of the Requirement to elect a species**

Applicant traverses this requirement for an election of species. First, it is noted that the claims in this application have been searched. An Office Action on the merits has been received, the closest prior art cited, and a response thereto was filed a year and a half ago. The claims were rejected under 35

U.S.C. §102 and/or 35 U.S.C. §103(a) over June *et al.* or June *et al.* in view of Cracauer. June et al. teaches a method for inducing a population of T cells to proliferate by providing a first signal to activate the cells and then a second signal to stimulate proliferation. This is essentially all that June et al. shows. Cell densities substantially greater than $10^6$ are not disclosed, nor are populations of cells produced that could be clinically used.

June et al. does not disclose or teach a method in which selected populations of cells are produced. June et al. does not disclose expansion of cells to produce stable populations of effector cells (as defined in the instant specification i.e. TIL cells, LAK cells etc.), nor does June et al. disclose production of stable populations of regulatory immune cells. As defined and described in the instant specification (see, e.g., page 19):

> regulatory immune cells that produce IL-2 and IFN-$\gamma$, but do not produce IL-4 are Th1" cells. Regulatory immune cells that produce IL-4 and IL-10, but do not produce IFN-$\gamma$ are termed "Th2" cells. Regulatory immune cells that produce TGF-$\beta$, IL-10 and IFN-$\gamma$, but do not produce IL-2 or IL-4 are termed "Th3" cells. Populations of cells that produce a majority of Th1 cytokines are designated "Th1-like"; populations producing a majority of the Th2 cytokines are designated Th2-like"; those producing a majority of Th3 cytokines are designated "Th3-like". Thus, each composition, although containing a heterogeneous population of cells, will have the properties that are substantially similar, with respect to cytokine, to the particular Th subset.

Example 6 on pages 31-32 of June et al. shows that the cytokine profiles produced by the cells are not characteristic of a population of cells that fit any of the above profiles, nor do the populations appear to be stable, since the lymphokine profile changes over time and the cells end up producing an array of cytokines characteristic of mixtures of cells. Thus, June et al. does not disclose a method in which the starting population is directed to a selected stable population that could be used for clinical treatment as described in the instant application. Therefore, for these reasons and the reasons of record, June et al. does not anticipate any of the instant claims. In addition to the above-noted

claims, added claims 193-195 clearly capture a distinction between the instant application and the disclosure of June et al.

As noted, June et al. teaches a method of growing T lymphocytes, CD4+ and CD8+ T cells at relatively low cell densities of about 1 x $10^5$ cells/ml- 0.5 x $10^6$ cells/ml using a combination of mitogenic antibodies in the absence of IL-2. June et al., however, does not teach or suggest a method for obtaining clinically relevant numbers of T lymphoid cells nor expansion of such cells under conditions that produce high cell density, an element recited in all of the claims. Furthermore, with respect to certain claims (see, e.g., claim 192) June et al. does not teach or suggest growth under conditions in which differentiated populations are produced.

With respect to claims 17, 22-25 and 31-35, all of which require expansion of regulatory T cells, June et al. also does not teach or suggest a method of producing regulatory T cells nor a method whereby the regulatory T cells are expanded under conditions that produce high cell density to result in clinically relevant numbers of cells. At most, June et al. teaches activation and growth of CD4+ cells using anti-CD3 + anti-CD28 and evaluation of the cytokines produced. These cells do not have a stable cytokine profile (see page 31, lines 26-29), and represent a heterogeneous population. As discussed above, simple measurement of cytokine production does not meet the definition of a regulatory immune cell as used in the specification (page 19, lines 4-19).

Hence, the issues of obviousness and anticipation of the claims over the closest prior art of which applicant or the Office are aware have been addressed.

Second, the Examiner urges that the methods use different types of T cells and has divided the claims on this basis and also on the basis of the intended use of the cells. The starting material is material that comprises mononuclear cells, the methods produce different types of T cells, depending

upon the activators selected. All of the resulting cells can be used for autologous therapy.

Also, the different groups identified by the Examiner contain overlapping subject matter. As described in the application, methods for generating clinically relevant numbers of effector immune cells and of regulatory immune cells are provided. In particular, methods for generating substantially homogeneous populations of clinically relevant numbers of regulatory immune cells, including Th1 and Th2 cells, as well as Th1-like and Th2-like mononuclear cell populations are provided.

Also provided are methods for producing clinically relevant quantities (i.e., therapeutically effective numbers, typically greater than $10^9$, preferably greater than $10^{10}$) of autologous specific T cell types for treatment of disease states where a relative deficiency of such cells is observed.

Hence the claims reflect the discovery of a method for directing differentiation of mononuclear cells to a particular regulatory T cell type.

Third, if this division of claims is maintained, then applicant ultimately could be granted five patents, that include claims with overlapping subject matter. For example, claim 197 is directed to:

> 197. A method for generating a high density of clinically relevant numbers of T lymphoid cells, comprising:
> collecting material comprising body fluid or tissue containing mononuclear cells from a mammal;
> treating the cells under conditions whereby *ex vivo* differentiation of cells into selected regulatory immune cells is induced; and
> contacting, in the absence of exogenous interleukin-2, the material with two or more activating proteins specific for cell surface proteins present on cells in the material and in an amount sufficient to induce *ex vivo* cell expansion, whereby the cells expand in number.

Claim 22 is directed to:

> 22. (Amended) A method for generating clinically relevant cell numbers of regulatory T lymphoid cells, comprising:
> (a) collecting material containing mononuclear T lymphoid cells from a mammal;

(b) activating the cells to alter their cytokine production profile; and

(c) inducing cell proliferation and expanding the cells under conditions that produce high cell density of at least about $10^9$ cells/liter and produce clinically relevant number of regulatory T lymphoid cells.

155. A method for generating clinically relevant numbers of regulatory T lymphoid cells for autologous cell therapy, comprising:

(a) collecting material comprising body fluid or tissue containing mononuclear cells from a mammal;

(b) treating the cells to induce differentiation of mononuclear cells into regulatory T cells, wherein regulatory T cells are mononuclear cell that have the ability to control or direct an immune response, but do not act directly as effector cells in the response; and

(c) contacting the resulting differentiated cells with one or more activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce *ex vivo* cell expansion, whereby clinically relevant numbers of regulatory cells for autologous cell therapy are generated.

Each of these claims could ultimately end up in different patents, since they have been identified as "patentably distinct species". Obvious-type double patenting of claims of the later issuing patents could not be held over the earlier issuing patents. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Fourth, an election of species requirement is intended as a search tool for use in situations, such as organic chemistry cases with a multitude of R groups, where there are too many species to search. In such instances, the applicant is entitled to have a reasonable number (typically 5 to 10) of species searched. In this instance, without conceding the propriety of the identified "species", only a limited number of so-called species have been identified. Searching of all of the so-called species would not be unreasonable, particularly, since the case has already been searched.

Therefore, reconsideration and withdrawal of the election of species requirement is respectfully requested.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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